Amendments to the Claims:

This listing of the claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently amended) A method for screening for an agent that modulates BMP-mediated signaling, comprising:

(a) contacting

(i) a ~~first polypeptide comprising a~~ HECT E3 ubiquitin ligase WW domain, wherein the domain comprises[[;]] SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13~~, or a variant thereof in which the ability of the polypeptide to bind to a Smad protein is not substantially diminished relative to the HECT E3 ubiquitin ligase~~;

(ii) a ~~second polypeptide comprising a~~ Smad PY motif, wherein the motif comprises [[;]] SEQ ID NO:14, 15, 16, 17, 20, 21, 22, 23, 24, or 25~~, or a variant thereof in which the ability of the polypeptide to bind to an E3 ubiquitin ligase is not substantially diminished relative to a native Smad protein comprising the PY motif~~; and

(iii) a candidate agent;

under conditions that permit a detectable level of binding of the ~~first polypeptide~~ HECT E3 ubiquitin ligase WW domain to the ~~second polypeptide~~ Smad PY motif in the absence of the candidate agent; and

(b) comparing the level of binding of the ~~first polypeptide~~ HECT E3 ubiquitin ligase WW domain to the ~~second polypeptide~~ Smad PY motif in the presence of the candidate agent to a control level of binding of the ~~first polypeptide~~ HECT E3 ubiquitin ligase WW domain to the ~~second polypeptide~~ Smad PY motif in the absence of candidate agent, and therefrom determining whether the candidate agent modulates BMP-mediated signaling.

2. (Previously presented) The method according to claim 1, wherein the HECT E3 ubiquitin ligase WW domain comprises the sequence:

Gly-Pro-Leu-Pro-Xaa-Gly-Trp-Glu-Xaa-Xaa-Xaa-Taa-Taa-Taa-Gly-Taa-Xaa-Tyr-Tyr-Haa-Xaa-His-Asn-Thr-Taa-Thr-Thr-Taa-Trp-Xaa-Taa-Pro-Taa (SEQ ID NO:2);
wherein each Taa is an independently selected polar amino acid residue, Haa is a hydrophobic residue and each Xaa is an independently selected amino acid residue.

3. (Previously presented) The method according to claim 1, wherein the Smad PY motif comprises the sequence Ser/Thr-Pro-Pro-Pro-Pro/Ala/Gly-Tyr (SEQ ID NO:15), wherein

Ser/Thr is an amino acid residue that is serine or threonine and Pro/Ala/Gly is an amino acid residue that is selected from the group consisting of proline, alanine and glycine.

4. (Currently amended) The method according to claim 3, wherein the Smad PY motif comprises the sequence ~~Thr-Pro-Pro-Ala-Tyr~~ Thr-Pro-Pro-Pro-Ala-Tyr (SEQ ID NO:16), ~~or~~ Thr-Pro-Pro-Pro-Gly-Tyr (SEQ ID NO:18) or Pro-Ala-Asp-Thr-Pro-Pro-Pro-Ala-Tyr-Leu/Met-Pro-Pro-Pro-Asp (SEQ ID NO:17), wherein Leu/Met is an amino acid residue that is leucine or threonine.

5. (Previously presented) The method according to claim 1, wherein the candidate agent is a small molecule within a combinatorial library.

6. (Currently amended) The method according to claim 1, wherein the ~~first polypeptide~~ HECT E3 ubiquitin ligase WW domain is immobilized on a solid support and the ~~second polypeptide~~ Smad PY motif comprises a tag.

7. (Currently amended) The method according to claim 1, wherein the ~~second polypeptide~~ Smad PY motif is immobilized on a solid support and the ~~first polypeptide~~ HECT E3 ubiquitin ligase WW domain comprises a tag.

8. (Previously presented) The method according to claim 6 or claim 7, wherein the tag is biotin or a radioactive group.

9. (Previously presented) The method according to claim 1, wherein the level of binding is determined via a two-antibody sandwich assay.

10. (Previously presented) The method according to claim 1, wherein the level of binding is determined via a competitive assay.

11.-54. (Cancelled)

55. (Previously presented) The method according to claim 2, wherein each Taa is selected from the amino acid residue group consisting of Ser, His, Pro, Asp, Glu, Thr, and Tyr.

56. (Previously presented) The method according to claim 2, wherein each Haa is selected from the hydrophobic residue group consisting of Ile, Val, Leu, and Met.

57. (Currently amended) The method of claim 1, wherein:

(i) when the level of binding of the ~~first polypeptide~~ HECT E3 ubiquitin ligase WW domain to the ~~second polypeptide~~ Smad PY motif is increased as compared to the control level, the agent decreases BMP-mediated signaling, or

(ii) when the level of binding of the ~~first polypeptide~~ HECT E3 ubiquitin ligase WW domain to the ~~second polypeptide~~ Smad PY motif is decreased as compared to the control level, the agent increases BMP-mediated signaling.

58. (Previously presented) The method of claim 1, wherein said determining whether the candidate agent modulates BMP-mediated signaling further comprises the step of measuring

or otherwise determining the level of Smad ubiquitination in the presence of the agent as compared to in the absence of the agent, wherein:

(i) an increase in Smad ubiquitination indicates the agent decreases BMP-mediated signaling, or

(ii) a decrease in Smad ubiquitination indicates the agent increases BMP-mediated signaling.

59. (Previously presented) The method of claim 1, wherein said determining whether the candidate agent modulates BMP-mediated signaling further comprises the step of measuring or otherwise determining the level of Smad protein in the presence of the agent as compared to in the absence of the agent, wherein:

(i) an increase in Smad protein indicates the agent increases BMP-mediated signaling, and

(ii) a decrease in Smad protein indicates the agent decreases BMP-mediated signaling.

60. (New) The method of claim 1, wherein said HECT E3 ubiquitin ligase WW domain consists of the amino acid sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13.

61. (New) The method of claim 1, wherein said Smad PY motif consists of SEQ ID NO:14, 15, 16, 17, 20, 21, 22, 23, 24, or 25.

62. (New) The method of claim 1, wherein said HECT E3 ubiquitin ligase WW domain consists of the amino acid sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13; and wherein said Smad PY motif consists of SEQ ID NO:14, 15, 16, 17, 20, 21, 22, 23, 24, or 25.